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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WALLENHORST, MAUREEN	

ART UNIT	PAPER NUMBER
1743	

DATE MAILED: 10/22/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/091,440	Applicant(s) TSUCHIDA ET AL.	
	Examiner Maureen M. Wallenhorst	Art Unit 1743	

-- Th MAILING DATE of this communication appears on th cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner. (abstract)

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4, 9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. Applicants are notified, however, that a copy of PCT/JP00/05512 and an English language translation of this application have not been received. Applicants are requested to file a copy of PCT/JP00/05512 and an English language translation of this application (published in Japanese) so that the Examiner may determine the common subject matter between the instant application and the PCT application, and determine what filing date the instant application is entitled to. Until the PCT application and the English translation of said application are received, the filing date of the instant application for the purpose of applying prior art against the claims under 35 USC 102 and 35 USC 103 will be considered March 7, 2002.

2. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 250 words. It is important that the abstract not exceed 250 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

3. The abstract of the disclosure is objected to because of the inclusion of legal phraseology such as "comprising". Correction is required. See MPEP § 608.01(b).

4. Claims 8-9 and 19-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 is indefinite since the units for the molecular weight of polyoxyethylene are not clear. Is the recited molecular weight range in units of Daltons or another unit of molecular weight? See this same problem in claim 19.

Claim 9 is indefinite since the molecular assemblies have not been positively recited as containing lipid therein. Therefore, the recitation of the amount of polyoxyethylene with respect to the total amount of lipid in the molecular assemblies is not clear. See this same problem in claim 20.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-20, 22-23 and 26-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Sakai et al (from Bioconjugate Chemistry, vol. 11, pages 425-432, April 21, 2000).

Sakai et al teach of an oxygen infusion comprising hemoglobin vesicles containing hemoglobin therein, and a method for preserving the hemoglobin vesicles. The surface of the

hemoglobin vesicles is modified with polyethylene glycol (PEG) chains (i.e. a polyoxyethylene), which serves to improve the dispersion state of the vesicles. In addition, the PEG-modified hemoglobin vesicles show an improved blood circulation and tissue oxygenation due to the absence of hemoglobin vesicle aggregate formation and viscosity elevation. The PEG is present in an amount of 0.3% mol of the lipids in the outer surface of the vesicles. The PEG is inserted into the lipid bilayer of the vesicles. The vesicles are then preserved by removing oxygen from the suspension containing the vesicles (i.e. deoxygenation), and converting the hemoglobin to the deoxy-form. This step is performed by bubbling nitrogen through the suspension and storing the suspension in an oxygen-impermeable container filled with inert gas (i.e. nitrogen). Deoxygenation serves to prevent metHb formation in the vesicles. A physiological reductant such as homocysteine can also be contained in the suspension. Sakai et al teach that the suspension of hemoglobin vesicles subjected to PEG modification followed by deoxygenation makes it possible to store a hemoglobin suspension at ambient temperature (23^0C) for 1 year, or at 40^0C for 6 months.

8. Claims 1-2, 5, 13, 15, 17 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Sakai et al (see abstract from Jinko Ketsueki, vol. 7, no. 4, pages 105-110, 1999).

Sakai et al teach of a method for preserving an oxygen infusion containing hemoglobin vesicles, which is achieved by polyoxyethylene conjugation and deoxygenation. The method comprises the steps of modifying the surface of the vesicles with polyoxyethylene, and deoxygenating the suspension with nitrogen bubbling. The samples stored at 4 degrees and 23 degrees show a stable dispersion state for 1 year. The vesicles also contain a physiological reductant (i.e. homocysteine) therein.

9. Claims 1-4, 6, 13-17, 21 and 26-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Nho (WO 92/08478, submitted in the Information Disclosure Statement filed on March 7, 2002).

Nho teaches of a method for preserving hemoglobin products, including those which have been chemically modified, as well as hemoglobin within living cells. Chemically modified hemoglobin products include those which have been conjugated to polyalkylene oxide. The polyalkylene oxide can be polyethylene glycol (i.e. a polyoxyethylene). The chemically modified hemoglobin product is preserved by exposing the hemoglobin to an inert gas via a gas permeable membrane, such that the inert gas passes through the membrane in order to come into contact with the hemoglobin. This process serves to deoxygenate the hemoglobin product. The deoxygenated hemoglobin is then stored in a closed vessel filled with nitrogen. Since the steps of the method taught by Nho (i.e. chemical modification of a hemoglobin composition with polyoxyethylene followed by deoxygenation) are the same as those recited in the instant claims, the hemoglobin compositions taught by Nho also inherently exhibit no loss of oxygen transport function after storage either at 40 degrees for six months or at 23 degrees for one year, similar to the instant invention.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claims 7-12 and 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nho in view of Sakai et al (reference AAW on the Information Disclosure Statement filed March 7, 2002). For a teaching of Nho, see previous paragraphs in this Office action. Nho fails to teach that the chemically modified hemoglobin is modified by fixing the polyoxyethylene to the surface of the hemoglobin product (i.e. to the surface of the cell membrane containing hemoglobin therein).

Sakai et al teach of a method for modifying the surface of hemoglobin vesicles by fixing polyethylene glycol-conjugated phosphatidylethanolamine to the surface of the vesicles. The molecular weight of the PEG ranges from 2000 to 5000. The PEG attaches to a hydrophobic moiety on the hemoglobin vesicles. Sakai et al teach that the PEG modification of hemoglobin vesicles serves to suppress intervesicular aggregation and cause prompt flow in vessels, thus suggesting that PEG modified hemoglobin vesicles have the potential for efficient oxygen supply.

Based upon the combination of Nho and Sakai et al, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to chemically modify the hemoglobin products taught by Nho by fixing polyoxyethylene to the surface of the hemoglobin product,

similar to the method taught by Sakai et al, since Sakai et al teach that this type of modification to hemoglobin products serves to prevent aggregation of the vesicles holding the hemoglobin and serves to improve flow in vessels for efficient oxygen supply. It also would have been obvious to one of ordinary skill in the art to vary the concentration of the polyoxyethylene used to modify the hemoglobin products taught by Nho to the level recited in the instant claims since concentration is a result effective variable that can be experimentally varied in accordance with the optimization of a particular method and the achievement of a desired result.

13. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nho in view of Estep (WO 89/06969; submitted in the Information Disclosure Statement filed on March 7, 2002). For a teaching of Nho, see previous paragraphs in this Office action. Nho fails to teach that the hemoglobin product contains a physiological reducing agent therein.

Estep teaches of a hemoglobin solution, which is deoxygenated, and combined with a chemical reducing agent. The reducing agent serves to maintain the hemoglobin in the deoxygenated state.

Therefore, based upon a combination of Nho and Estep, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the deoxygenated hemoglobin product taught by Nho with a physiological reducing agent since Estep teaches that a reducing agent serves to help maintain a hemoglobin solution in a deoxygenated state.

14. Claims 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nho in view of Applicants' admitted prior art in the specification. For a teaching of Nho, see previous paragraphs in this Office action. Nho fails to teach that the hemoglobin product can be a

hemoglobin vesicle, a lipid heme vesicle, a lipid-heme-triglyceride microsphere or an albumin-lipid heme.

Applicants admit on pages 2-3 of the instant specification that hemoglobin vesicles, lipid-heme vesicles, lipid-heme-triglyceride microspheres and albumin-lipid heme vesicles are known in the art, and have been previously synthesized and studied for their ability to reversibly bind oxygen.

Therefore, based upon the combination of Nho and Applicants' admitted prior art, it would have been obvious to one of ordinary skill in the art to use one of hemoglobin vesicles, lipid-heme vesicles, lipid-heme-triglyceride microspheres or albumin-lipid heme vesicles as the hemoglobin product taught by Nho that is subjected to polyoxyethylene modification followed by deoxygenation since Applicants admit that these are all known hemoglobin products that have been assayed and confirmed for their ability to reversibly bind oxygen, and the hemoglobin product disclosed by Nho must be able to reversibly bind oxygen for use in an infusion.

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Please make note of: Nho et al (US Patent nos. 5,234,903 and 5,386,014), Farmer et al (US Patent nos. 4,911,929 and 4,776,991), Winslow et al and JP 4-5242 which all teach of hemoglobin products used for oxygen transport.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maureen M. Wallenhorst whose telephone number is 703-308-3912. The examiner can normally be reached on Monday-Wednesday from 6:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden, can be reached on (703) 308-4037. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0661.

Maureen M. Wallenhorst
Primary Examiner
Art Unit 1743

mmw

October 14, 2003

Maureen M. Wallenhorst
MAUREEN M. WALLENHORST
PRIMARY EXAMINER
GROUP [redacted] 1700